

REMARKS

Upon entry of the instant amendment, claims 1, 3, 5-7, 9-10 and 12-14 will remain pending in the above-identified application and stand ready for further action on the merits.

The instant amendment does not introduce any new matter into the application as originally filed and at the same time serves to simplify issues for appeal or otherwise put the case into better form for consideration by the United States Patent Office Board of Appeals. As such entry of the instant amendment at present is respectfully solicited.

In support of the Applicants' contention that the instant amendment does not incorporate new matter into the application as originally filed, the following is noted.

Support for currently amended claims 1, 3, 7 and 10, occurs in original claims 2, 4, 8 and 11, respectively, and disclosure occurring in the specification at page 48, lines 9-13. The amendment of claims 5-6, simply corrects the dependency of these claims, as claim 4 has been cancelled herein.

Enclosed 37 CFR § 1.132 Declaration

Enclosed with the present response is a second 37 CFR § 1.132 Declaration of Mr. Yasushi Ochiai, one of the present co-inventors. The accompanying Declaration has been prepared and

signed by Mr. Ochiai to evidence that patentable differences and distinctions exist between the present invention as claimed and the disclosure of Pierre et al. (US 5,300,318). In this respect, the enclosed declaration is pertinent to the Examiner's outstanding rejection under 35 USC § 103(a) set forth below, and a full review thereof is thus respectfully requested. The Examiner is also requested to fully review the accompanying declaration, in as much as all Comparative Testing set forth therein is supportive of the patentability of the present claims.

The accompanying declaration of Mr. Ochiai in certain portions references Mr. Ochiai's earlier filed 37 CFR § 1.132 declaration (filed with the USPTO with the Applicants' prior response of November 18, 2003). As such, the Examiner is also respectfully requested to fully review and reconsider Mr. Ochiai's earlier filed 37 CFR § 1.132 declaration at this time.

Claim Rejections Under 35 USC § 103

Claims 1-14 are rejected under 35 USC § 103(a) as being unpatentable over Pierre et al. (US 5,300,318). Reconsideration and withdrawal of this rejection is respectfully requested based upon the following remarks and the submission herewith of the accompanying Declaration of Mr. Yasushi Ochiai under 37 CFR § 1.132.

First, to the extent that the present rejection pertains to cancelled claims 2, 4, 8 and 11, it has been rendered moot, as these claims have been cancelled herein.

Present Invention and Its Advantages

The present invention relates to a method of manufacturing drug granules, and more particularly provides a pharmaceutical preparation containing a water-soluble drug as an active ingredient at a high density, which shows superior stability in a uniform content.

In the method of manufacturing a drug granule as instantly claimed, a granulation step occurs "of spraying a solution of a water soluble drug on a crystal of said water soluble drug substantially without using a binder or in the absence of binder in a rotary fluidized bed granulate coating apparatus, wherein the drug granule has a granular strength of 650-2500 gf/mm²." (See claim 1, *emphasis added*.)

An important aspect of the present invention relates to the granular strength of the granules, since it allows for the granules to be "tableted" or subjected to a "tableting" step, without breaking of the granules. This aspect of the present invention is also significant when the claimed inventive methods

also contain a step of "coating said drug granule with a release control film coating agent." (See claims 7, 9-10 and 14.)

Distinctions Over the Cited Art

The above aspects of the present invention are nowhere taught, disclosed or otherwise rendered obvious by the disclosure of Pierre et al. (US '318). For example, Pierre et al. (US '318) does not provide any suggestion regarding granular strength and/or tableting of coated granules.

In contrast to the teachings of Pierre et al. (US '318), the present invention provides granules having sufficient granule strength to be capable of maintaining a coating film during tableting processes, and thereby also allow for the manufacture of tablets from the coated granules having desirable and suitable dissolution characteristics. On this point, the Examiner is invited to review Mr. Ochiai's accompanying Declaration, particularly the Figures and Tables provided therein, as well as Mr. Ochiai's earlier filed 37 CFR § 1.132 declaration (filed with the USPTO on November 18, 2003).

The method of claim 1 can also be distinguished from Pierre et al., since a "rotary fluidized bed granulate coating apparatus" is used by present inventors, which is different from the type of granulator taught by Pierre et al., and produces non-

expected results when compared with Pierre et al. More particularly, unlike instant claim 1, which recites the use of a rotary fluidized bed granulator (when a binder is present), Pierre uses an Uniglatt apparatus (which is a *non-rotary* fluidized bed coating device).

Further, there is provided no teaching or any information in the cited Pierre et al. reference that would lead one to the unexpected results that are associated with the present invention. Which unexpected results are, namely, that a difference in *resistance ability to acid solution* is achieved with the present invention that is not envisioned, obtained or otherwise rendered obvious by the teachings and disclosure of Pierre et al.

Still further, even if one skilled in the art were to assume that generally speaking, the density of a granulate from a rotary fluidized bed granulator is much higher than that obtained from a fluidized bed coating device; nonetheless, in the cited Pierre et al. cited art reference, there is provided no information about granular strength and/or properties of coated granules, and importantly, there are not obtained the advantageous results that are associated with the instant invention as claimed.

As also evidenced in the accompanying Declaration of Mr. Ochiai, test results provided show that the granular strength of

the present inventive granules is quite distinct and different from that of Pierre et al. (US '318). The results show that a difference exists with regard to the inner structure of the granules between the present invention and Pierre et al.

More particularly, as set forth in the accompanying Ochiai 37 CFR § 1.132 declaration (at pages 7-12 thereof):

Figures 1-4 show that the granules of the present invention have homogeneous structure. Figures 7-10 show that the granules of Pierre et al. (US 5,300,318) have porous and non-homogeneous structure. Figures 11-14 show the lysine granules of Pierre et al. after polishing have smooth surfaces, but the inner part of the polished granules still has porous and non-homogeneous structure. Figure 5 shows that the granules of the present invention have smooth and homogeneous surfaces. Figure 15 shows that coated granules of Pierre et al. having smooth and homogeneous surfaces. Figures 6 and 16 show that coated granule of the present invention and Pierre et al. have almost same thickness of coating agent. Figure 17 is a graph showing the results of the dissolution test of the coated lysine granules of the present invention. Figure 18 is a graph showing the results of the dissolution test of the coated lysine granules of Pierre et al.

It is desirable for an enteric preparation that its dissolution rate for 1 to 2 hours is less than 5 % in the solution of pH 1.2. A 30 % coating ratio is sufficient for the granules of the present invention to meet this goal. Thus, the coated granules of present invention show an excellent ability as an enteric preparation for human use, as shown in Figure 17 of the enclosed Ochiai Declaration. However, even a 60% Coated granules of Pierre et al. do not show enough resistant ability to the solution of pH 1.2, as shown in Figure 18 of the enclosed Ochiai Declaration.

The test results provided in the enclosed Ochiai 37 CFR § 1.132 Declaration show that the resistant ability to the solution of pH 1.2 of the present invention is quite distinct and different from that of Pierre et al. (US 5,300,318). The difference of the results is considered to be from the property of granules between the present invention and Pierre et al. During the coating process the strength of granules of Pierre et al. is not strong enough. It is considered that the granules of Pierre et al. are worn away during the coating process and small particles of active ingredient are produced. The small particles is considered to exist in and on the enteric coated layer of the granules of Pierre et al. and to dissolve into the solution.

Notably, as Mr. Ochiai states in his enclosed declaration at page 12, "I believe that those result and difference between the granule of the present invention and the granules of Pierre et al. is unexpected and that the present invention is not obvious from Pierre et al. for the man skilled in the art."

Accordingly, based upon a consideration of the above remarks and the comparative test results in Mr. Ochiai's accompanying 37 CFR § 1.132 Declaration and the remarks set forth above, it follows that the outstanding rejection under 35 USC § 103(a) of claims 1-14 over Pierre et al. (US '318) must now be withdrawn.

CONCLUSION

Based upon the remarks presented herein, as well as the comparative testing results and conclusions based thereon set forth in Mr. Ochiai's accompanying 37 CFR § 1.132 Declaration, the Examiner is respectfully requested to issue a Notice of Allowance clearly indicating that each of the pending claims 1, 3, 5-7, 9-10 and 12-14 are allowable at present.

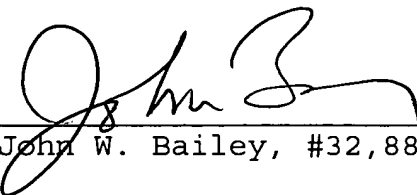
Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Appl. No. 10/091,559

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment(s): 37 CFR § 1.132 Declaration of Mr. Yasushi Ochiai